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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 09/691,776 | 10/18/2000 | Carolyn E. Mountford | 1274/60326/PJP | 3709 |

7590 09/09/2003

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| EXAMINER | |
|---|---|
| SODERQUIST, ARLEN | |
| **ART UNIT** | **PAPER NUMBER** |
| 1743 | 9 |

DATE MAILED: 09/09/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/691,776 | MOUNTFORD ET AL. | |
| | Examiner | Art Unit | |
| | Arlen Soderquist | 1743 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the corresp ndence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *13 June 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-26* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *6-8* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

1. Claims 1-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over MacKinnon (*Radiology*, **1997**) in view of Somorjai (*Magnetic Resonance in Medicine*, **1995**). In the paper MacKinnon discusses fine-needle biopsy specimens of benign breast lesions distinguished from invasive cancer ex vivo with proton MR spectroscopy. To determine whether invasive breast cancer can be distinguished from benign lesions with proton magnetic resonance (MR) spectroscopy ex vivo on the basis of altered cellular chemistry. Two hundred eighteen fine-needle biopsy specimens were obtained in 191 patients undergoing surgery and were analyzed with proton MR spectroscopy. MR spectroscopic and histopathologic findings were compared. Invasive carcinoma produced increased signal at 3.25 ppm, attributable to choline-containing metabolites. Discrimination between invasive carcinoma (n = 82), benign lesions (n = 106), or carcinoma in situ (n = 17) was based on the resonance intensity at 3.25 ppm standardized to the resonance at 3.05 ppm (P lt .001). The ratio of peak height intensities of resonances at 3.25 to those at 3.05 ppm was less than 1.7 in 102 of the 106 normal or benign lesions. All carcinoma in situ specimens with comedonecrosis or a microinvasive component (n = 6) were categorized at MR spectroscopy with invasive carcinoma, while others with in situ disease alone were categorized with benign lesions (n = 11). The sensitivity and specificity of MR spectroscopy in fine-needle biopsy specimens in distinguishing benign lesions from invasive cancer were 95% and 96%, respectively. The paper concluded that proton MR spectroscopy of fine-needle biopsy

specimens provides objective diagnostic information that complements findings of conventional preoperative investigations of breast lesions. relative to the instant claims is the paragraph bridging the columns 2-3 of page 664. The last sentence of the paragraph cites the Somorjai reference and teaches that the multivariate techniques of the reference are "likely to improve sensitivity and specificity" of the analysis.

In the paper Somorjai presents computerized consensus diagnosis as a classification strategy for the robust analysis of $^{1}H$ MR spectra of thyroid neoplasms. They developed and applied a new classification strategy called computerized consensus diagnosis (CCD). Its purpose is to provide robust, reliable classification of biomedical data. The strategy involves the cross-validated training of several classifiers of diverse conceptual and methodological origin on the same data, and appropriately combining their outcomes. In the paragraph that bridges pages 258-259 the formation of training and testing sets from the data is explained. The training set was cross validated by the leave-one-out method in which one fewer than the total number of samples are included in the training set, classifying the excluded sample and repeating the procedure until each sample has been excluded from the reduced training set. The test set is then classified with an optimal classifier that was retrained on all of the samples in the training set. The strategy is tested on proton magnetic resonance spectra of human thyroid biopsies, which are successfully allocated to normal or carcinoma classes. They used Linear Discriminant Analysis, a Neural Net-based method, and Genetic Programming as independent classifiers on two spectral regions, and chose the median of the six classification outcomes as the consensus. The use of the leave-one-out method in the Linear Discriminant Analysis is taught on page 259 on the last paragraph of the left column. The paragraph bridging pages 260-261 teaches the formation of multiple training sets along with the reasons therefore. The paragraph bridging pages 261-262 teaches that because of this cross validation method each individual sample in the test set has a probability assigned relative to the class that it belongs. This procedure yielded 100% specificity and 100% sensitivity on the training sets, and 100% specificity and 98% sensitivity on samples of known malignancy in the test sets. They discuss the necessary steps any classification approach must take to guarantee reliability, and stress the importance of fuzziness and undecidability in robust classification. The last page presents further refinements that would reduce some of the problems or improve some of the results.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate the multivariate analysis methodology of Somorjai into the MacKinnon analysis of breast tissues because of the statement by MacKinnon directing one to the Somorjai multivariate method as likely to provide improved results and the teaching of improved analysis results by Somorjai.

2. Applicant's arguments filed June 13, 2003 have been fully considered but they are not persuasive. The argument that the Somorjai reference does not teach repeating the cross validation step or the weighted average can best be answered by looking at the reference. In the paragraph that bridges pages 258-259 the formation of training and testing sets from the data is explained. The training set was cross validated by the leave-one-out method in which one fewer than the total number of samples are included in the training set, classifying the excluded sample and repeating the procedure until each sample has been excluded from the reduced training set. The test set is then classified with an optimal classifier that was retrained on all of the samples in the training set. The paragraph bridging pages 260-261 teaches the formation of multiple training sets along with the reasons therefore. Thus the cross validation procedure is performed a number of times for each training set. The paragraph bridging pages 261-262 teaches that because of this cross validation method each individual sample in the test set has a probability assigned relative to the class that it belongs. This would indicate some sort of a weighted average for the formation of the optimal classifier that is used on the test set of samples.

3. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

4. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. The additional reference is related to the investigation of cancer tissues by magnetic resonance spectroscopy (MRS) and the use of MRS to identify cancerous tissues.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Arlen Soderquist whose telephone number is (703) 308-3989. The examiner's schedule is variable between the hours of about 5:30 AM to about 5:00 PM on Monday through Thursday and alternate Fridays.

For communication by fax to the organization where this application or proceeding is assigned, (703) 305-7719 may be used for official, unofficial or draft papers. When using this number a call to alert the examiner would be appreciated. Numbers for faxing official papers are 703-872-9310 (before finals), 703-872-9311 (after-final), 703-305-7718, 703-305-5408 and 703-305-5433. The above fax numbers will generally allow the papers to be forwarded to the examiner in a timely manner.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0661.

Arlen Soderquist

September 4, 2003

ARLEN SODERQUIST
PRIMARY EXAMINER